Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nebris Steri-Neb 300 mg/5 ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One single-dose 5 ml ampoule contains tobramycin 300 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

A clear to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nebris is used for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged six years and older with cystic fibrosis (CF).

The official guidance on the appropriate use of antibacterial agents should be considered.

Nebris is indicated in adults, adolescents and children aged six years and older.

4.2 Posology and method of administration

Nebris is for inhalation use and is not intended for parenteral use.

Posology

The recommended daily dose for adults and children is one ampoule twice daily for 28 days, with a dose interval as close as possible to 12 hours and not less than six hours. After completion of the 28-day treatment, patients should stop using Nebris for the next 28 days. Patients should maintain a cycle of 28 days of active treatment and 28 days of rest from treatment. Dosage is not adjusted for weight, so all patients should receive one ampoule of Nebris Steri-Neb 300 mg twice daily.

Nebris Dosing Regimen in Controlled Clinical Studies

Cycle 1		**Cycle 2**		**Cycle 3**	
28 days	28 days	28 days	28 days	28 days	28 days
Nebris 300 mg twice daily plus standard care	Standard care only	Nebris 300 mg twice daily plus standard care	Standard care only	Nebris 300 mg twice daily plus standard care	Standard care only

Data from controlled clinical studies, over a period of six months using the following regimens, have shown that the improvement in lung function was maintained above baseline during the 28-day rest period.

In addition, safety and efficacy have been assessed for up to 96 weeks (12 cycles). Safety and efficacy have not been assessed in patients under the age of six years, patients with forced expiratory volume in 1 second (FEV_1) <25% or >75% predicted, or in patients colonised with *Burkholderia cepacia*.

Therapy should be initiated by a physician with experience in the management of CF. Nebris treatment should be continued on a cyclical basis for as long as the physician considers that the patient is gaining clinical benefit from the inclusion of tobramycin into their standard treatment regimen. If there is clinical deterioration of the pulmonary status, additional anti-pseudomonal therapy should be considered. Data from clinical studies indicated that a microbiological report of *in vitro* drug resistance did not preclude necessarily, a clinical benefit for the patient.

Paediatric population

The safety and efficacy of tobramycin in children aged less than 6 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

The entire contents of one ampoule should be emptied into the nebuliser and administered by inhalation over an approximate 15-minute period using a commercially available hand-held PARI LC PLUS reusable Nebuliser with a suitable compressor. The compressor should deliver a flow rate of 4 – 6 L/min and/or a back pressure of 110 – 217 kPa when attached to the nebuliser. It is important that the manufacturer's instruction for care and use of the Nebuliser and Compressor are followed.

Nebris is inhaled whilst the patient is sitting or a standing upright posture and who is breathing normally through the mouthpiece of the nebuliser. The use of a nose clip may help the patient breathe through the mouth. When taking Nebris, it is important that the patient continues their standard regimen of chest physiotherapy. The use of appropriate bronchodilators should continue as deemed necessary. When patients are taking several different respiratory therapies it is recommended that they are taken in the following order: bronchodilator, chest physiotherapy, other inhaled medicinal products and, finally, Nebris.

Maximum tolerated daily dose
The maximum tolerated daily dose of tobramycin has not been established.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any other aminoglycoside.

4.4 Special warnings and precautions for use

General warnings
For information on fertility, pregnancy and lactation, see section 4.6.

Nebris should be used with caution in patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis.

Serum concentrations of tobramycin should only be measured in blood samples obtained by venipuncture. Finger-prick blood sampling is not recommended as it is not a validated method and it has been observed that contamination of the skin of the fingers from the preparation and nebulisation may lead to falsely increased serum levels of tobramycin. Furthermore, the contamination cannot be avoided by hand washing before testing.

Bronchospasm
Bronchospasm can occur with nebulised tobramycin, as is the case with other medicinal products. The first dose of tobramycin should be administered under supervision, using a pre-nebulisation bronchodilator if it is part of the patient's current regimen. FEV_1 should be measured before and after nebulisation. If there is evidence of therapy-induced bronchospasm in a patient not receiving a bronchodilator, then the test should be repeated on another occasion using a bronchodilator. If bronchospasm occurs in the presence of a bronchodilator, then an allergic response may be indicative and Nebris should be discontinued. Bronchospasm should be treated as medically appropriate.

Neuromuscular disorders
Nebris should be used with extreme caution in patients with neuromuscular disorders such as Parkinsonism and conditions characterised by myasthenia, including myasthenia gravis, as aminoglycosides may aggravate muscular weakness, because of a potential curare-like effect on neuromuscular function.

Nephrotoxicity
Although nephrotoxicty has been associated with parenteral aminoglycoside therapy, there was no evidence of nephrotoxicity during clinical trials with tobramycin.

The product should be used with caution in patients with known or suspected renal dysfunction and serum tobramycin concentrations should be monitored. Patients with severe renal impairmant i.e., serum creatinine >2 mg/dl (176.8 µmol/l), were not included in the clinical studies.

Current clinical practice suggests baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every six complete cycles of Nebris therapy (180 days of nebulised aminoglycoside therapy). If there is any evidence of nephrotoxicity, all tobramycin therapy should be discontinued until trough serum tobramycin concentrations fall below 2 µg/mL. Nebris may then be resumed at the physician's discretion. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate taking into account the risk of cumulative toxicity.

Ototoxicity
Ototoxicity is manifested as both auditory and vestibular toxicity and has been reported with parenteral aminoglycosides. Audiotoxicity, as measured by complaints of hearing loss or by audiometric evaluation did not occur with tobramycin treatment in controlled clinical studies. In open-label studies and post-marketing experience, some patients with previous or concomitant use of intravenous aminoglycosides experience hearing loss. Vestibular toxicity is manifested by vertigo, ataxia or dizziness. Physicians should consider the potential aminoglycosides to cause cochlear or vestibular toxicity and to carry out appropriate assessments of auditory function during tobramycin treatment. In patients with a predisposing risk of ototoxicity due to previous, systemic aminoglycoside therapy, it may be necessary to consider audiological assessment prior to starting tobramycin treatment. Furthermore, the onset of tinnitus, which is a symptom of ototoxicity, warrants caution. If a patient reports occurrence of tinnitus or hearing loss, the physician should refer the patient for audiological assessment. Patients receiving concomitant parenteral aminoglycoside therapy should be appropriately monitored taking into account the risk of toxicity.

Haemoptysis
Inhalation of nebulised solutions may induce a cough reflex. The use of Nebris in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Microbial resistance
Some patients receiving Nebris show an increase in aminoglycoside Minimum Inhibitory Concentrations of *P. aeruginosa* isolates tested. There is a theoretical risk that patients being treated with nebulised tobramycin may develop *P. aeruginosa* isolates resistant to intravenous tobramycin (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking Nebris together with dornase alfa, β-agonists, inhaled corticosteroids and other oral and parenteral anti-pseudomonal antibiotics demonstrated an adverse event profile similar to those of the control group.

Concurrent or sequential use of Nebris with other medicinal products with nephrotoxic or ototoxic potential should be avoided. Some diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. In particular, Nebris should not be administered concomitantly with furosemide, urea or mannitol.

Amphotericin B, cefalotin, ciclosporin, tacrolimus and polymixins increase the potential toxicity of parenterally administered aminoglycosides.

Platinum compounds can lead to the increased risk of nephrotoxicity and ototoxicity.
Anticholinesterases and botulinum toxin can enhance the neuromuscular effects.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Tobramycin should not be used during pregnancy or lactation unless the benefits to the mother outweigh the risks to the

foetus or baby.

Fertility
No effect on male or female fertility was observed in animal studies after subcutaneous administration (see section 5.3).

Pregnancy
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). There are no adequate data from the use of inhaled tobramycin in pregnant women. Aminoglycosides can cause foetal harm including congenital deafness when high systemic concentrations are achieved in pregnant woman. Nebris should not be used during pregnancy or lactation unless the benefits to the mother outweigh the risks to the foetus or baby. If Nebris is used during pregnancy or if the patient becomes pregnant while using Nebris, she should be informed of the potetntial hazard to the foetus.

Breast-feeding
Systemic tobramycin is excreted in breast milk; however, it is not known whether inhaled tobramycin will achieve sufficiently high serum concentrations to be detected in breast milk. A decision should be made whether to terminate breast feeding or discontinue Nebris, because of the potential for ototoxicity and nephrotoxicty in infants.

4.7 Effects on ability to drive and use machines

Nebris has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In controlled clinical trials, voice alteration and tinnitus were the only undesirable effects reported in significantly more patients treated with tobramycin than in the control group; (13% tobramycin vs 7% control) and (3% tobramycin vs 0% control), respectively. The episodes of tinnitus were transient and resolved without discontinuation of tobramycin therapy; the incidence of tinnitus was not associated with permanent loss of hearing on audiogram testing. The risk of tinnitus did not increase with repeated cycles of exposure to tobramycin.

Additional undesirable effects, some of which are common sequelae of the underlying disease, but where a causal relationship to tobramycin could not be excluded were: sputum discolouration, respiratory tract infection, myalgia, nasal polyps and otitis media.

Frequency estimate: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000), not known (cannot be estimated from the available data).

MedDra – system organ class	**Frequency and Symptom**
Infections and infestations	*Rare:* - Laryngitis
	Very rare: - Oral candidiasis, fungal infection
Blood and lymphatic system disorders	*Very rare:* - Lymphadenopathy
Immune system disorders	*Very rare:* - Hypersensitivity
Metabolism and nutrition disorders	*Rare:* - Anorexia
Nervous system disorders	*Rare:* - Dizziness, headache, aphonia *Very rare:* Somnolence
Ear and labyrinth disorders	*Rare:* - Tinnitus, hearing loss *Very rare:* - Ear disorder, ear pain
Respiratory, thoracic and mediastinal disorders	*Uncommon:* - Dysphonia, dyspnoea, cough, pharyngitis *Rare:* - Bronchospasm, chest discomfort, productive cough, lung disorder, haemoptysis, epistaxis,

	rhinitis, asthma *Very rare:* - Hyperventilation, hypoxia, sinusitis
Gastrointestinal disorders	*Rare:* - Dysgeusia, nausea, mouth ulceration, vomiting *Very rare:* - Diarrhoea, abdominal; pain
Skin and subcutaneous tissue disorders	*Rare:* - rash *Very rare:* - Urticaria, pruritus
Musculoskeletal and connective tissue disorders	*Rare:* - Back pain
General disorders and administration site conditions	*Rare:* Asthenia, pyrexia, chest pain, pain *Very rare:* - Malaise
Investigations	*Rare:* - Pulmonary function test decreased

In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss (see section 4.4). Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see section 4.3 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via ‘freepost’, in addition to the traditional post-paid ‘yellow card’ option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
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Tel: +353 1 6764971
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Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Inhalation of tobramycin results in low systemic bioavailability. Symptoms of aerosol overdose may include severe hoarseness.

In the event of accidental ingestion of Nebris, toxicity is unlikely to occur as tobramycin is poorly absorbed from the gastrointestinal tract.

In the case of inadvertent intravenous administration of Nebris, signs and symptoms of parenteral tobramycin overdose may occur, which include dizziness, tinnitus, vertigo, loss of hearing, respiratory distress and/or neuromuscular blockade and renal impairment.

In the event of acute toxicity, treatment includes immediate withdrawal of tobramycin and baseline renal function testing. Serum tobramycin concentrations may be helpful in monitoring overdose. In the case of overdosage, the possibility of drug interactions with alterations in the elimination of tobramycin or other medicinal products should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside Antibacterials, ATC code: J01GB01

Mechanism of action
Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. Its mechanism of action is primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Mechanism of resistance
Resistance to tobramycin can occur via several mechanisms including: alterations of the ribosomal subunit within the bacterial cell, interference with the transport of tobramycin into the cell and inactivation of tobramycin by several enzymes (for example, adenylylating, phosphorylating and acetylating enzymes). Cross resistance to other aminoglycosides may also occur.

Breakpoints
The breakpoints, as mentioned below, are based on systemic tobramycin use and might not be applicable to nebulised tobramycin. In accordance with CPMP/EWP/558/95 rev 1, the following Minimum Inhibitory Concentration (MIC) breakpoints are defined for tobramycin by EUCAST (European Committee on Antimicrobial Susceptibility Testing Version 1.1.2010).

Enterobacteriaceae	S ≤ 2 mg/L, R > 4 mg/L
Pseudomonas spp.	S ≤ 4 mg/L, R > 4 mg/L
Acinetobacter spp.	S ≤ 4 mg/L, R > 4 mg/L
Staphylococcus spp.	S ≤ 1 mg/L, R > 1 mg/L
Non-species related	S ≤ 2 mg/L, R > 4 mg/L

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. As necessary, active advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

The organisms associated with pulmonary infections in CF that may be expected to respond to inhaled tobramycin are as follows:

Susceptible	*Pseudomonas aeruginosa* *Haemophilus influenzae* *Staphylococcus aureus*
Insusceptible.	*Burkholderia cepacia* *Stentrophomonas maltophilia* *Alcaligenes xylosoxidans*

Information from clinical studies

The local biological activity of nebulised aminoglycosides is inhibited by the sputum from patients with CF. Therefore, the sputum concentration of aerosolised tobramycin needs to be around 10 and 25%, respectively, above the MIC for *P. aeruginosa* growth suppression and bactericidal activity, respectively. In controlled clinical trials, 97 % of patients receiving inhaled tobramycin achieved sputum concentrations 10 fold the highest *P. aeruginosa* MIC cultured from the patient and 95% of patients receiving tobramycin achieved 25 fold the highest MIC. Clinical benefit is still achieved in a majority of patients with culture strains with MIC values above the parenteral breakpoint.

Most patients with *P. aeruginosa* isolates with tobramycin MICs < 128 µg/ml at baseline showed improved lung function after treatment with inhaled tobramycin. Patients with a *P. aeruginosa* isolate with a MIC ≥ 128 µg/ml at

baseline are less likely to show a clinical response. However, seven of 13 patients (54 %) in the placebo-controlled studies who acquired isolates with MICs ≥ 128 µg/ml while using inhaled tobramycin had improved lung function.

Inhaled tobramycin showed a small but clear increase in tobramycin, amikacin and gentamycin MIC for *P. aeruginosa* isolates tested. Each additional six months of treatment resulted in incremental increases similar in magnitude to that observed in the six months of controlled studies. The most prevalent aminoglycoside resistance mechanism seen in *P. aeruginosa* isolated from chronically infected CF patients is impermeability, defined by a general lack of susceptibility to all aminoglycosides. *P. aeruginosa* isolated from CF patients has also been shown to exhibit adaptive aminoglycoside resistance that can be characterised by a reversion to susceptibility when the antibiotic is removed.

Other information

There is no evidence that patients treated for up to 18 months with inhaled tobramycin were at greater risk for acquiring *B. cepacia*, *S. maltophilia* or *A. xylosoxidans*, than would be expected in patients not treated with tobramycin. *Aspergillis* species were more frequently recovered from the sputum of patients receiving tobramycin; however, clinical sequelae such as Allergic Bronchopulmonary Aspergillosis were rarely reported with similar frequency as in the control group.

There are insufficient clinical safety and efficacy data in children < 6 years of age.

In an open-label uncontrolled study, 88 patients with CF (37 patients between 6 months and 6 years, 41 patients between 6 and 18 years of age and 10 patients above 18 years of age) with early (non-chronic) *P. aeruginosa* infection were treated for 28 days with tobramycin. After 28 days, patients were randomised 1:1 to either stop (n=45) or to receive a further 28 days treatment (n=43).

Primary outcome was the median time to recurrence of *P. aeruginosa* (any strain) which was 26.1 and 25.8 months for the 28-day and 56-day groups, respectively. It was found that 93 % and 92 % of the patients were free of *P. aeruginosa* infection 1 month after the end of treatment in the 28-day and 56-day groups, respectively. The use of tobramycin with a dosing regimen longer than 28 days continuous treatment is not approved.

5.2 Pharmacokinetic properties

Absorption and distribution

Sputum concentrations: Ten minutes after the first inhalation of Nebris 300 mg, the average sputum concentration of tobramycin was 1,237 µg/g (range: 35 to 7,414 µg/g). There is no accumulation of tobramycin in the sputum; after 20 weeks of therapy with the tobramycin regimen, the average sputum concentration of tobramycin 10 minutes after inhalation was 1,154 µg/g (range: 39 to 8,085 µg/g). High variability of sputum tobramycin concentrations was observed. Two hours following inhalation, sputum concentration declined to approximately 14 % of the 10 minute measurement.

Serum concentrations: The median serum concentration of tobramycin, one hour after inhalation, was 0.95 µg/ml (range: below the limit of quantitation to 3.62 µg/ml). After 20 weeks of therapy, the median serum tobramycin concentration, one hour after dosing, was 1.05 µg/ml (range: below the limit of quantitation to 3.41 µg/ml).

Elimination

The elimination of tobramycin administered via inhalation has not been studied.

Systemically absorbed tobramycin is eliminated principally by glomerular filtration with an elimination half life of approximately two hours. Less than 10 % is bound to plasma proteins.

Unabsorbed tobramycin is probably eliminated in expectorated sputum.

5.3 Preclinical safety data

Pre-clinical data reveal that the main hazards for humans based on safety pharmacology, repeated dose toxicity, genotoxicity, or reproductive toxicity, are nephrotoxicity and ototoxicity. In repeat-dose studies, toxicity is targeted at the kidneys and vestibular/cochlear function. Toxicity is seen at much higher systemic concentrations than are achievable by inhalation at the recommended clinical dose.

No reproductive toxicity studies have been performed with nebulised tobramycin. Subcutaneous administration of tobramycin 100 mg/kg/day in rats and the maximum tolerated dose of 20 mg/kg/day in rabbits, during organogenesis, was not found to be teratogenic. Teratogenicity could not be assessed at higher parenteral doses in rabbits due to maternal toxicity and abortion.

Based on available data from animals, a risk of toxicity (e.g., ototoxicity) during prenatal exposure cannot be excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Water for Injections
Sulphuric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be diluted with any other medicinal products in the nebuliser.

6.3 Shelf life

2 years

The foil pouches (intact or opened) may be stored at up to 25ºC for up to 28 days.

The contents of the whole ampoule should be used immediately after opening (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2 – 8ºC). Do not freeze. Store in the original package to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

Tobramycin solution may be slightly yellow and some variability in colour may be observed; this does not indicate loss of activity providing the solution has been stored as recommended.

6.5 Nature and contents of container

Nebris Steri-Neb is supplied as 5 ml single-dose low density polyethylene ampoules.
Four ampoules are packed and sealed in a foil pouch. Each carton comprises 14 (56 ampoules), 28 (112 ampoules) or 42 (168 ampoules) foil pouches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is a sterile, non-pyrogenic, aqueous preparation for single-use only. As it is preservative-free, the contents of the whole ampoule should be used immediately after opening and unused solution discarded. Opened ampoules should never be stored for re-use. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/153/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 03rd August 2012

10 DATE OF REVISION OF THE TEXT

October 2013